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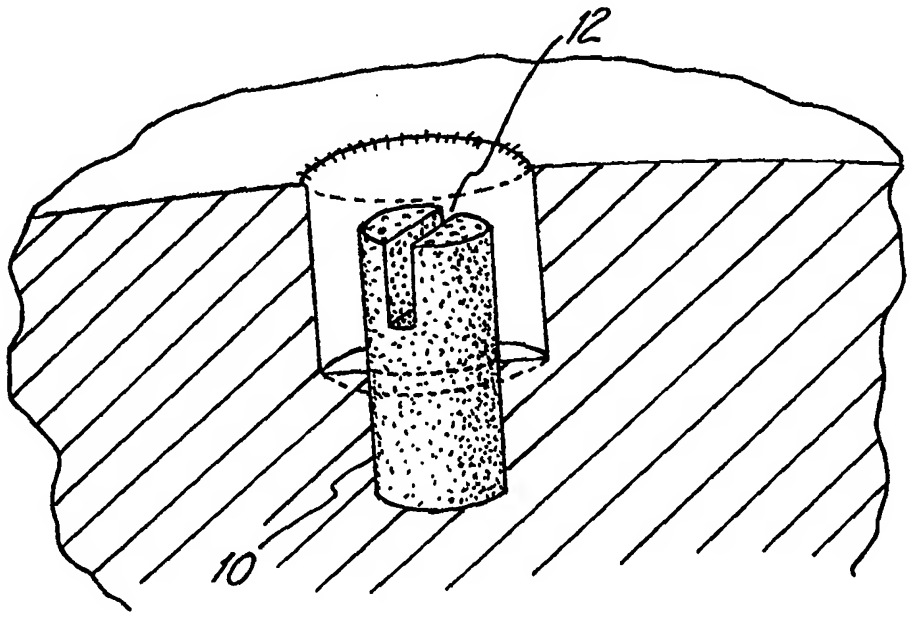
(54) Title: POROUS COMPOSITE BIOMATERIAL AND BIOPOLYMER SYSTEM

(57) Abstract

A surgical system that includes a flowable, curable biopolymer and a porous, implantable anchor biomaterial, the anchor material being adapted (e.g., in terms of porosity and chemical compatibility) to permit the flowable biopolymer to infiltrate some or all of the material's pores and there cure in order to retain and anchor the resultant composite material. The composite material can be adapted to encourage new bone ingrowth, in order to stabilize the retention of the implant over extended use. In one embodiment the biopolymer comprises the components of a polyurethane and the porous anchor material comprises a reticulated open cell carbon foam infiltrated with tantalum by a process of chemical vapor deposition (CVD).



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POROUS COMPOSITE BIOMATERIAL AND BIOPOLYMER SYSTEM

TECHNICAL FIELD

In one aspect, the present invention relates to methods and apparatuses for resurfacing or repairing orthopedic joints. In another aspect the invention relates to cancellous bone substitutes.

BACKGROUND OF THE INVENTION

Applicant has previously described a system for repairing orthopedic tissues (e.g., resurfacing joint surfaces) that includes the step of delivering a curable two-part biopolymer by minimally invasive means. See, for instance, US Patent No. 5,556,429 and PCT Application No. PCT/US97/00457, the disclosures of each of which are incorporated herein by reference. In one embodiment, such a system can be used to resurface the knee, e.g., by a method that involves the use of minimally invasive means to form one or more anchor points within the subchondral bone of the tibial surface, and thereafter delivering a flowable, curable biopolymer, adapted to be cured *in situ* in order to fill the anchor points and resurface the joint. The anchor points can be of any suitable configuration, and can be prepared using a variety of techniques, e.g., by the use of arthroscopic drill bits.

On a separate subject, Kaplan, US Patent No. 5,282,861 (the disclosure of which is incorporated herein by reference) is representative of the type of approach in

which cancellous autografts have been used in orthopedic applications to provide a porous framework within which revascularization occurs and against which new bone is layered. Such materials can also provide a population of osteoprogenitor cells and a complement of bone growth-inducing factors. Grafting, however, requires surgery to obtain the material, and a viable substitute is desirable.

In turn, a specialty science devoted to the study of substances utilized for implants in medicine and dentistry, biomaterials, has taken tremendous strides in the last 20 years. Matching the requisite biomechanical requirements for an implant with the environment of surrounding tissues has been a formidable challenge. Significant progress was made in resolving this problem in the early 1970's, when the importance of porosity was first recognized. Later work showed that certain physical parameters of the porosity affect the type of tissue and the rate of ingrowth. The degree of interconnectivity and the nominal pore size were found to be critical factors in determining the success of an implant. Maximum interconnectivity, or the absence of "dead ends", was found to facilitate ingrowth. These studies showed that pore sizes less than 10 microns prevent ingrowth of cells; pore sizes of 15–50 microns encourage fibrovascular ingrowth; pore sizes to 50–150 microns result in osteoid formation; and pore sizes of greater than 150 microns facilitate the ingrowth of mineralized bone.

Bone ingrowth into the voids of a porous material provides ideal skeletal fixation for the permanent implants used for the replacement of bone segments lost due to any number of reasons, or in total joint prostheses. Biological compatibility, intimate contact with the surrounding bone, and adequate stability during the early period of bone ingrowth have been identified as important requirements, along with proper porosity. The optimal porous material should have good crack resistance, particularly under impact, and a compliance comparable to that of bone. The material should also make the manufacture of implants of precise dimensions easy, and permit the fabrication of either thick or thin coatings on load-bearing cores.

One common prerequisite for successful ingrowth is that the implant be placed next to viable bone. In fact, the presence of bone within the implant has become presumptive evidence of osteoconductive properties: that is, the ability of bone to grow into a porous structure when the structure is placed next to bone. Initially, the cells that interface the implant convert to bone, then the front of regenerated bone

progresses into the implant. This process is known as osseointegration, meaning the achievement of direct contact between living bone and implant.

The research, development, and manufacture of synthetic porous implants having the physical properties required to promote bone ingrowth have proved to be a major endeavor. Implants with porous surfaces of metallic, ceramic, polymeric, or composite materials have been studied extensively over the last two decades. The above-captioned '861 patent describes a tantalum open cell structure formed by chemical vapor deposition onto a reticulated carbon substrate. The resultant lightweight, strong, porous structure mimics the microstructure of natural cancellous bone and acts as a matrix for the incorporation of bone *in vivo*.

BRIEF DESCRIPTION OF THE DRAWING

In the Drawing:

Figure 1 shows a biomaterial of the present invention in the form of a generally cylindrical dowel-pin device, having a slot adapted to be filled with biomaterial; and

Figure 2 shows an alternative structure in which a dowel-pin device is provided with a circumferential groove and threads.

SUMMARY OF THE INVENTION

The present invention provides a surgical system for preparing a composite material *in situ*, the system comprising a unique combination of a flowable, curable biopolymer and a porous, implantable biomaterial. The biomaterial is preferably fabricated to form an anchor material that is adapted (e.g., in terms of structure, porosity and chemical compatability) to permit it to be positioned within bone and to permit at least a portion of it to be filled and/or infiltrated with flowable biopolymer in order to provide a mechanical lock between the two. In such an embodiment, the resulting cured composite is initially retained in position within the bone, largely by virtue of its mechanical properties, where the porosity of its biomaterial component serves to encourages new bone ingrowth over time. Bone ingrowth, in turn, serves to further stabilize the retention of the implant over extended use, and thereby improve its performance.

The mechanical lock between biopolymer and biomaterial can be formed in any suitable manner, e.g., by the infiltration of curing biopolymer into pores of the biomaterial itself, and/or by filling the biopolymer into grooves or other structures within the biomaterial. Once in place within the biomaterial, the biopolymer is able to fully cure in order to retain and anchor the resultant composite material. In so doing, the composite material (and preferably the anchor component thereof) is adapted to encourage new bone ingrowth, in order to stabilize the retention of the implant over extended use and improve its performance. In a preferred embodiment the biopolymer comprises the components of a polyurethane and the porous anchor material comprises a reticulated open cell carbon foam infiltrated with tantalum by a process of chemical vapor deposition (CVD).

The composite is preferably positioned in temporary or permanent touching, or bonded, contact with bone. In other aspects, therefore, the invention provides a method of preparing and using such a system, as well as kits and/or components adapted to perform such a method. In yet another aspect, the invention provides a composite material comprising a biomaterial filled and/or infiltrated, at least in part, with a cured biopolymer and having bone ingrown into at least some of its pores, the composite being positioned within an orthopedic site, e.g., within or in apposition to a bone surface.

Examples of suitable anchor materials include calcium hydroxyapatite (HA), as well as nonmetallic materials adapted for use in porous form for implants, including the ceramics tricalcium phosphate (TCP), calcium aluminate, and alumina, carbon; various polymers, including polypropylene, polyethylene, and polyoxymethylene (delrin); and ceramic-reinforced or -coated polymers. Ceramics, while strong, are less preferred since they tend to be brittle and often fracture readily under loading. Polymers, in turn, while possessing good ductility, are also less preferred since they tend to be weak.

Metals, and metal-containing materials, are particularly preferred since they tend to combine high strength and good ductility, making them attractive candidate materials for implants (and effectively the most suitable for load-bearing applications). Many dental and orthopedic implants contain metal, and are useful in the present system, most often titanium or various alloys such as stainless steel or

vitallium (cobalt-chromium-molybdenum). Ceramic-coated metals are also useful, e.g., HA or TCP on titanium. While conventional metallic biomaterials can be used (e.g. stainless steel, cobalt-based alloys), they are less preferred in that they do not easily lend themselves to fabrication into porous structures.

Examples of other suitable materials are described, for instance, in Higgins et al., US Patent No. 5,008,159, for "Method of producing silicon carbide-based bodies", and in Smith et al., US Patent No. 5,697,932 for "Bone graft delivery system and method". The '159 patent describes silicon carbide-based bodies produced by forming a porous compact of silicon carbide, a carbide of a metal, and carbon, and infiltrating the compact with a molten mixture comprising the metal and silicon. The metal may be selected from: titanium, zirconium, hafnium, molybdenum, niobium, tantalum, tungsten, and vanadium, and the infiltration temperature may be between 1900° C. and 2100° C. The '932 patent, in turn, describes a surgical technique for the delivery of bone graft material to a medullary canal and implantation of a prosthetic device includes placing bone graft material into an elongate hollow tube and arranging a plunger having an elongate rod portion into the hollow tube.

In a particularly preferred embodiment, a carbon foam is infiltrated as a vapor in the process of chemical vapor deposition (CVD). The resulting lightweight, strong, porous structure, mimicking the microstructure of natural cancellous bone, acts as a matrix for the incorporation of bone or reception of cells and tissue. The pores of the matrix are preferably connected to one another to form continuous, uniform channels with no dead ends. This intricate network of interconnected pores provides optimal permeability and a high surface area to encourage cell and tissue ingrowth, vascularization, and deposition of new bone.

The result is a biomaterial composite that, when placed next to bone or tissue and infiltrated in part with flowable biopolmer, initially serves as a prosthesis and anchor, and then functions, at least in part, as a scaffold for regeneration of normal tissues. The new biomaterial composite fulfills the need for an implant modality that has a precisely controllable shape and at the same time provides an optimal matrix for cell and bone ingrowth as well as biopolymer infiltration. Additionally, the physical and mechanical properties of the porous metal structure can be specifically tailored to the particular application at hand.

While certain preferred porous materials are strong, and have an elasticity close to trabeculated bone, it is particular preferred that once placed within the bone, and following bone ingrowth, the resultant material have a modulus that approximates that of surrounding bone. Presently preferred materials therefor exhibit a porosity (or portions that provide a plurality or continuum of porosities) in order to provide an optimal combination of such properties as polymer permeation and final modulus. A particularly preferred porous biomaterial includes a plurality of portions of varying porosities, including for instance, an outermost portion adapted to positioned within or adjacent to corresponding cartilage) a pore size particularly conducive to polymer permeation, followed by a portion having a pore size adapted to enhance cortical bone (and to be positioned within or adjacent to subchondral bone); and finally, one or more pore sizes adapted to match the modulus of surrounding trabeculated bone, and to be positioned therein.

In this manner, one can achieve a variety of properties, including a porous structure that minimizes the presence of material (e.g., metal); a modulus transition between the material and bone that substantially covers the entire surface below the polymer in order to minimize side loading modulus mismatch; the ability to be permeated by a polymeric substance having any desired viscosity (e.g., between about 10,000 and about 200,000 poise); and the ability to create creates a continuous modulus transition between the polymer and the core material, by varying the pore size accordingly.

Tantalum is preferred as the material of choice based on its good mechanical properties, excellent corrosion resistance, and demonstrated biocompatibility. Tantalum (atomic number 73, atomic weight 180.95, density 16.68 g/cm^3) is a transition element (periodic group VB), a highly refractory (melting point 2996° C.), strong, ductile metal with excellent oxidation and corrosion resistance. Early evidence of excellent tissue acceptance, combined with low corrosion, has led to the use of tantalum as a surgical implant material and its use in a variety of applications, including pacemaker electrodes, wire, foil and mesh for nerve repair, cranioplasty plates, contrast media for airwave radiographic studies, radiopaque markers for following bone growth, ligation clips, and more recently on an experimental basis in femoral endoprostheses.

It should be noted that niobium, which has similar chemical and mechanical properties to tantalum, may also be used as well as appropriate alloys of tantalum and niobium. For example, other metals such as niobium, hafnium and/or tungsten could be alloyed with the tantalum or hafnium and/or tungsten with niobium to change modulus and/or strength. Therefore, any reference to tantalum is not meant to be an exclusion of other metals.

The crystal structure of tantalum is body-centered and cubic, giving it excellent ductility due to the six possible slip planes. It is corrosion-resistant and resists the attack of most chemical agents; tantalum pacemaker electrodes have exhibited excellent corrosion resistance both *in vitro* and *in vivo*. This inertness likely accounts for the good tissue compatibility of the base metal as well, whereas a noble metal such as gold, though considered corrosion-resistant, is not sufficiently biocompatible due to its catalytic surface.

Tantalum does not inhibit cell growth and indeed becomes tightly enveloped by new osseous tissue soon after implantation, whereas dental gold and cobalt-based alloys can inhibit cell growth and cause bone resorption. With tantalum, osseous ingrowth has been demonstrated by others right up to and into implants. Complete, strong, long-term osseointegration has been demonstrated with tantalum implants in both dental and orthopedic applications, under both unloaded and heavily loaded conditions, for implantation periods as long as eight to twelve years.

In addition, tantalum has an elastic modulus close to that of bone, much closer than any of the other high-strength metals and alloys commonly used for implants; this too may well contribute to the favorable reaction with bone. With its greater ductility, excellent corrosion resistance, good workability, and demonstrated biocompatibility, tantalum is a preferred material for use in a system of the present invention, combined with one or more biopolymers as described herein.

DESCRIPTION OF THE PREFERRED EMBODIMENT

A system of the present invention is particularly well suited for use in delivering an anchor material and a curable biomaterial (i.e., biopolymer) composition by minimally invasive techniques to a tissue site within the body. As used herein the following words and terms shall have the meanings ascribed below:

"repair" will refer to the use of a composition to augment, replace or provide some or all of the structure or function of natural tissue *in vivo*, for instance, to provide an implant such as a catheter, or to repair (e.g., reconstruct or replace) natural tissue such as cartilage, e.g., fibrocartilage or hyaline cartilage present in a diarthroidal or amphiarthroidal joint. Repair can take any suitable form, e.g., from patching the tissue to replacing it in its entirety, preferably in a manner that reconstructs its natural or other desired dimensions;

"cure" and inflections thereof, will refer to any chemical, physical, and/or mechanical transformation that allows a composition to progress from a form (e.g., flowable form) that allows it to be delivered to the joint site, into a more permanent (e.g., cured) form for final use *in vivo*. When used with regard to the method of the invention, for instance, "curable" can refer to uncured composition, having the potential to be cured *in vivo* (as by catalysis or the application of a suitable energy source), as well as to a composition in the process of curing (e.g., a composition formed at the time of delivery by the concurrent mixing of a plurality of composition components). As further described herein, the cure of a composition can generally be considered to include three stages, including (a) the onset of gelation, (b) a period in which gelation occurs and the composition becomes sufficiently tack-free to permit shaping, and (c) complete cure to the point where the composition has been finally shaped for its intended use; and

"minimally invasive" refers to surgical techniques, such as microsurgical or endoscopic or arthroscopic surgical techniques, that can be accomplished with minimal disruption of the pertinent musculature, for instance, without the need for open access to the tissue injury site or through minimal incisions (e.g., incisions of less than about 4 cm and preferably less than about 2 cm). Such techniques are typically accomplished by the use of visualization such as fiberoptic or microscopic visualization, and provide a post-operative recovery time that is substantially less than the recovery time that accompanies the corresponding open surgical approach.

Biopolymer

Biopolymers suitable for use in the present invention can be provided in any suitable form, e.g., as two or more individual components. Some or all of these components can be provided either within or upon the body portion itself (e.g., in

attachable syringe cartridges) or remote therefrom (e.g., as canisters attached or attachable by tubing to the body portion itself). The onset of flow of the components, and in turn their mixing, is preferably controlled by the user, e.g., by actuating a mechanical delivery means or by making electrical contact. In a further preferred embodiment, e.g., the invention provides for a plurality of different biopolymers, the delivery of any or all being connectable and controllable by the user. Optionally, the user can control the types or relative amounts of various components being delivered, e.g., to provide for mixed biopolymer compositions having different desired (cured or curing) properties. The components for a two-component biopolymer source, for instance, can be predetermined to be mixed in any suitable order and ratio, e.g., in a 1:1 (volume to volume) ratio, or between about 1:10 or 10:1.

The term "biopolymer source", as used herein, will refer to the actual component containment vessels (e.g., canisters or syringes) themselves, as well as associated supports, tubing, controls and the like, for use in attaching the containment vessels to the body portion and delivering their contents to the inlet end of the mixing path. In turn, a device of this invention can be manufactured, used and sold either with the biopolymer source in attached or attachable form (e.g., in the form of the syringes described herein), or without the biopolymer source (e.g., in the form of the gun assembly described herein). In the event the device is provided without the biopolymer source, the user will typically provide a separate single-use or stock supply of the biopolymer, which will be attached to the device at or near the time of use. In such a case, the biopolymer source can be flowably attached to the device at the time of use and in a sterile manner.

A system of the invention preferably includes a biopolymer composition having two or more parts, where the parts can be combined at the time of use in order to initiate cure. A preferred biopolymer composition for use in a device of this invention is a curable polyurethane composition comprising a plurality of parts capable of being sterilized, stably stored, and mixed at the time of use in order to provide a flowable composition and initiate cure. In a particularly preferred embodiment, the parts include: (1) a quasi-prepolymer component comprising the reaction product of one or more polyether polyols, one or more isocyanates, and one or more reactive hydrophobic additives, and (2) a curative component comprising one

or more polyether polyols, one or more chain extenders, one or more catalysts, and optionally, other ingredients such as an antioxidant and dye. Upon mixing, the composition is sufficiently flowable to permit it to be delivered to the body using a device as described herein, and fully cured within the body under physiologically acceptable conditions. Preferably, the component parts are themselves flowable, or can be rendered flowable (e.g., by heating), in order to facilitate their mixing and use.

In a preferred embodiment, within the prepolymer, the polyether component is present at a concentration of between about 2% and about 10 %, and preferably between about 4% and about 8% by weight, based on the weight of the composition, and is selected from the group consisting of linear or branched polyols with polyether backbones of polyoxyethylene, polyoxypropylene, and polytetramethylene oxide (polyoxytetramethylene), and copolymers thereof. A particularly preferred polyol is polytetramethylene oxide, preferably of relatively low molecular weights in the range of 250 daltons to 2900 daltons, and combinations thereof.

In a further preferred embodiment the isocyanate is present in excess in the prepolymer component, e.g., at a concentration of between about 30% and about 50%, and preferably between about 35% and about 45%, by weight. The isocyanate is preferably an aromatic (poly)isocyanate selected from the group consisting of 2,2'- , 2,4'- , and 4,4'-diphenylmethanediisocyanate (MDI), and combinations thereof. In such an embodiment, the reactive polymer additive itself is present at a concentration of between about 1% and about 50% by weight, and is selected from the group consisting of hydroxyl- or amine-terminated compounds selected from the group consisting of poybutadiene, polyisoprene, polyisobutylene, silicones, polyethylenepropylenediene, copolymers of butadiene with acryolnitrile, copolymers of butadiene with styrene, copolymers of isoprene with acrylonitrile, copolymers of isoprene with styrene, and mixtures of the above. In a particularly preferred embodiment the additive comprises hydroxyl-terminated polybutadiene, present at a concentration of between about 5% and about 30%, by weight, and preferably between about 5% and about 20% by weight.

In a further preferred embodiment, the polyether polyol of the curative component is as described above with regard to the prepolymer and is present at a final concentration of between about 20% and 60%, and preferably between about

30% and about 45%, by weight. In such an embodiment, the chain extender comprises a combination of linear (e.g., cyclohexane dimethanol ("CHDM")) and branched (e.g, trimethyloyl propane ("TMP") chain extenders, with the former being present at a final concentration of between about 1% and 20 % (and preferably between about 5% and about 15%), and the latter being present at a final concentration of between about 1% and about 20%, and preferably between about 1% and about 10%, by weight of the final composition.

In a particularly preferred embodiment, a polymer system of this invention is provided as a plurality of component parts and employs one or more catalysts. The component parts, including catalyst, can be mixed to initiate cure, and then delivered, set and fully cured under conditions (e.g., time and exotherm) sufficient for its desired purpose. Upon the completion of cure, the resultant composition provides an optimal combination of properties for use in repairing or replacing injured or damaged tissue. In the course of curing, a suitable composition provides a bulk exotherm (within samples sizes suitable for *in vivo* use) of between about 100 degrees C and about 140 degrees C, and preferably between about 110 degrees C and about 130 degrees C, and a surface exotherm of between about 50 degrees C and about 80 degrees C, and preferably between about 60 degrees C and about 70 degrees C.

Additionally, a polymer system of the present invention preferably contains one or more, and more preferably two or more, biocompatible catalysts that can assist in controlling the curing process, including the following periods: (1) the induction period, (2) the setting period, and finally, (3) the final cure of the biopolymer. Together these three periods, including their absolute and relative lengths, and the rate of acceleration or cure within each period, determine the cure kinetics or profile.

The word "induction", and inflections thereof, when used in this respect refers to the time period between mixing or activation of one or more polymer components (under conditions suitable to begin the curing process), and the onset of gelation. In a method of the present invention, this period generally corresponds with the delivery of the biopolymer to the site of ultimate use. The induction period is characterized by infinitesimal or limited increase in viscosity of reacting mixture and relatively flat exotherm profile. Generally, a biopolymer of this invention is simultaneously mixed just prior to actual delivery into the joint site, providing the surgeon with sufficient

time to add and position material (e.g., into anchor points) before gelation causes the material to become less easily workable. Thereafter, the surgeon can leave the material in place as it sets, e.g., for on the order of three to twenty minutes, before placing instruments back into the site to finish sculpting the implant, or performing other desired steps such as positioning the femoral condyles to shape the implant.

The term "set time" (or gel time), as used herein, is determined from the initial mixing of components, and refers to the time needed for a mixed and delivered system to set to the point where it can be shaped. This period is characterized by a rapid rise in the slope of the reaction exotherm at the end of the period. By the end of this period, the surface of the gelled biopolymer is preferably tack free and will allow shaping, e.g., by positioning of the condyles. The "cure time", as used herein, is determined from the initial mixing, and refers to the total time needed to mix, shape and fully cure the biopolymer to the desired extent under the conditions used. Preferred polymer systems of this invention preferably provide an induction period that ends within about thirty seconds to two minutes following mixing of the components, followed by a set time of about 3 to about 15 minutes following mixing.

During the curing process (including both setting and completion of cure) the polymer system preferably exhibits an exotherm compatible for its intended use, e.g., preferably an exotherm of less than about 70 degrees C to about 90 degrees C, and more preferably less than about 80 degrees C. Given the present description, those skilled in the art will appreciate the manner in which the polymer system can be adjusted in a variety of ways to obtain suitable exotherm, during setting and cure, e.g., by the use of temperature dependent synergistic catalysis. Catalysts suitable for use in compositions of the present invention provide an optimal combination of such properties as set time, cure time, and in turn, viscosity (and flowability) of the curing polymer system.

In a particularly preferred embodiment, the selection of catalyst and other ingredients provides a cure profile that exhibits both synergistic and "delayed action" kinetics, in which induction of cure begins immediately upon mixing the polymer components, and is relatively "flat" during the induction period, without significant increase of viscosity of reaction mixture. This period permits delivery of the "flowable" polymer to the tissue injury site, and is followed by a setting period

characterized by variable increase in slope (in a plot of temperature vs. time) that is designed to quickly drive the curing process to completion, and in turn, to quickly provide a set polymer that is sufficiently strong and tack-free to permit final shaping.

The composition of the present invention can be delivered to a site within the body, and there fill or infiltrate at least a portion (e.g, groove or surface) of a porous biomaterial, e.g., one delivered prior to, with, after the delivery of the polymeric composition itself. The biopolymer can then be cured, preferably using minimally invasive means, in order to repair (e.g., reconstruct or resurface) tissue such as cartilage, and particularly cartilage associated with diarthroidal and amphiarthroidal joints. Optionally, the composition can be delivered and cured within an implanted mold device. A device as described herein can also be used to deliver biopolymer to a site within the body, e.g., to a mold or a site of damaged or diseased cartilage, to be cured *in situ* in order to provide an implant or repair the cartilage without undue surgical trauma.

The invention also provides a kit comprising both a porous biomaterial as described herein in combination with a plurality of sterile, flowable parts capable of being mixed at the time of use in order to provide a flowable composition and to initiate cure, the parts including: (1) a quasi-prepolymer component comprising the reaction product of one or more polyether polyols, one or more isocyanates, and one or more reactive hydrophobic additives, and (2) a curative component comprising one or more polyether polyols, one or more chain extenders, and one or more catalysts. The device can be used to mixed the quasi-prepolymer component and curative component, in order to deliver the mixture to a tissue site using minimally invasive means.

Optionally two or more biopolymer compositions can be delivered, e.g., sequentially, for instance to provide a biphasic or a heterogeneous cured material having varying properties, or to facilitate the ability of the biopolymer to infiltrate the pores of the biomaterial.

Various components of the present system, including the porous biomaterial and biopolymer source can be manufactured, sterilized, and sold alone, or sold together in a kit, e.g., with the biomaterial being provided in the form of a screw or

pin, and the biopolymer source adapted to be mixed at the time of use in order to initiate infiltration into the biomaterial and cure.

Porous Biomaterial

Cancellous, or spongy, bone is composed of a porous space-frame structure formed of open spaces defined by interconnected trabeculae, oriented along lines of principal stresses. At the microstructural level, the trabeculae are composed of layers of lamellar bone. Cancellous bone has anisotropic mechanical properties, i.e. different structural behavior along different orientations. Along the axis of the major channels, cancellous bone exhibits elastic behavior with sudden brittle failure at ultimate load in tension. When loaded with a tensile force whose line of action is skewed with respect to the channel axis of the bone, the stress-strain curve is parabolic with plastic deformation and greater energy absorption. It is therefore stiffer (has higher tensile and compressive moduli) but fails at a lower strain when loaded parallel to the predominant spicular direction than when loaded in other directions. These properties are important because they serve to absorb shock and distribute load in the vicinity of the articular surfaces of joints.

The porous material can be provided in any suitable form and having any suitable dimensions, e.g., in the form of beads, sheets, mesh, or formed objects such as a tapered or straight (and solid or hollow), shank, screw, bolt, nail, peg or dowel-pin that is delivered and secured earlier, and in the course of the same surgical procedure. The material is preferably adapted to be delivered to the site of repair and there positioned or anchored in permanent or temporary contact with bone or other appropriate bodily tissues, in a manner that permits the material to be permeated by polymer and, over time permit the ingrowth of tissue (e.g., bone). In embodiments in which the biomaterial is intended to fill one or more portions of the biomaterial, the biomaterial can be provided with one or more grooves, slits, or apertures of a suitable number, orientation and dimensions for their intended use. In a preferred embodiment, one or more of the same feature(s) that facilitate the initial placement of the porous biomaterial (e.g., screw slots) are also adapted to be filled with biomaterial in order to improve the stability of the composite formed by the two components.

An anchor material of the present invention can include portions or parts that vary considerably in terms of porosity, including some portions (e.g., non-bone

contacting portions) that are not porous at all, particularly when grooves or other means are used to provide an initial mechanical or chemical lock between biopolymer and biomaterial. The word "porous", and inflections thereof, as used to describe the biomaterial of the present invention, will generally refer to an anchor material having at least one surface adapted to be positioned within bone in order to encourage bone ingrowth.

Examples of such porous biomaterials are shown by reference to the Drawing, wherein Figure 1 shows a generally cylindrical, flat-headed biomaterial (10) having a slot (12) positioned centrally and perpendicular to the axis of the biomaterial, along the exposed head surface. The biomaterial is shown positioned within an anchor point drilled into the subchondral bone of the tibial surface of the knee joint. Upon filling the area with biopolymer (not shown) the biopolymer is able to fill the anchor point, as well as the groove, and including the tibial surface itself, in order to provide a permanent replacement articulating surface. Over time, bone is encouraged to grow into the portion of the biomaterial, thereby improving and ensuring the stability of the overall implant. Figure 2 shows a related embodiment, also within an anchor point in the knee, in which the biomaterial (20) provides a circumferential groove (22) adapted to positioned within the and filled by biopolymer. The lower portion of the biomaterial provides screw threads (24) that facilitate and secure its placement within the bone.

For embodiments in which the biopolymer is intended to infiltrate the biomaterial's pores (e.g., rather than filling grooves, etc.), an optimal balance is preferably achieved between the properties of the biopolymer itself (e.g., cure rate, viscosity) and those of the biomaterial (e.g., pore size, distribution and type (e.g., open, closed, interconnected)) and their interaction (e.g., relative hydrophobility/hydrophilicity, heat exchange conditions, hydraulic resistance, contact angle, capillary effects). Such a balance can be achieved by recognizing that the kinetics of the biopolymer viscosity change in the course of its cure. While the process itself can be complex, it may include an initial, and temporary, drop in viscosity due to the temperature increase (exotherm), followed by an increase in viscosity associated with the polymerization process itself. The cure kinetics can be affected by the catalyst level and type, temperature, conditions of heat exchange (e.g.,

size and shape of the biomaterial and/or its pores). Other means can be employed to facilitate infiltration, for instance, the use of coatings on the biomaterial to enhance its wettability to biopolymer, or the use of temporary extra pressure in the course of biopolymer delivery. The presence of body fluids in the surgical area, including in the pores themselves, can affect infiltration and cure characteristics and final properties of the cured composite material.

The pores can be formed at the time of forming the support material itself, or thereafter, for instance by the use of laser technology to create micro-pores in a pre-formed material. One company, for instance (Surface Technologies, Israel), has developed a laser surface texturing system to improve the performance of lubricated mechanical components. The system creates evenly distributed micro-pores on the mating surface. The micro-pores generate a hydrodynamic effect which significantly improves performance and durability. The system software includes a simulation model that enables the user to rapidly and accurately determine the optimal texturing settings for a given application, including the optimum pore diameter, depth, and distribution for any application.

Preferred biomaterials for use as substitutes for cancellous bone provide an optimal combination os such properties as elastic deformation and load distribution. In addition, the biomaterial will preferably not not produce load concentrations, particularly if placed close to the underlying surface of articular cartilage, which might increase the local stresses on the articular surface and lead to wear and damage of the surface. Cancellous bone demonstrates remodeling behavior according to Wolff's Law: that is, with the form being given, bone adapts to the loads applied to it. The converse is also true, and equally important: where loads are not applied, bone tends to resorb. An implant, then, must distribute stresses throughout its structure, the ingrowing bone, and the surrounding bone in order to avoid bone resorption and weakening caused by stress shielding.

The density of cancellous bone is 0.7 g/cm^3; its tensile modulus 0.2–0.5 GPa; tensile strength 10–12 MPa; and strain to failure 5–7%. Compared to cortical bone, cancellous bone is –¼ as dense (indicating its porous nature); 1/10–1/20 as stiff; and five times as ductile. The mechanical properties of the two types, though, actually

represent a continuum, reflecting the behavior of a relatively uniform material (bone) modified by differences in density and structure.

As described in the above-captioned US Patent No. 5,282,861, it appears from experiments with hydroxyapatite implants, that ingrowth and maturation of new bone are more rapid from a cancellous bone region than from cortical bone, with the tissue-implant interface reaching peak shear strength in dogs in 8 weeks. The process may take longer in humans, with remodeling still possible up to 2 years postoperation. Inadequate device designs may produce continued stress shielding remodeling as long as 9–10 years postoperation.

Biomaterials for osseous, or bone, implants are therefor preferably rigid and stress-resistant, while avoiding self-concentration of stresses that result in stress shielding. Also, osseous implants should ideally reside in the bone without interfering with bone remineralization, the natural process by which the body replenishes bone. The implant should be able to be precisely shaped and placed for optimal interface and performance. Finally, non-resorption would be a beneficial quality for implants used in load-bearing applications, and/or those in which complete bone ingrowth is not possible.

Preferably, the porous biomaterial is complete with respect to its interconnectivity, because constrictions between pores and isolated, deadend pockets can limit vascular support to ingrowing tissues; ischemia of the ingrowing bone cells results in failure of the implant. Incomplete vascularization or a reduction in the neovascularity also makes an implant vulnerable to bacterial colonization. Implants lacking completely interconnected porosity can also result in aberrant mineralization, stress shielding, low fatigue strength, and/or bulk displacement.

A preferred, open cell metal, structure of the present invention offers highly interconnected, three-dimensional porosity that is uniform and consistent, a structure exceptionally similar to that of natural cancellous bone. In this way it is superior to other porous metallic implant materials, whose "porosity" is artificially produced via some form of surface treatment that does not result in a truly complete, open porosity. Examples of these methods include macroscopic porous coatings (e.g. metal microspheres or wires sintered or otherwise attached to a bulk surface); microscopic

surface porosity (e.g. metal powder particles flame- or plasma-sprayed onto a bulk surface); and controlled surface undulations machined into a bulk surface.

Although certain porous ceramic materials do offer full porosity (e.g. the replamineform process for hydroxyapatite), they are presently less preferred than the metals as discussed previously. The open cell metal structure is osteoconductive, like other porous implants. Also, it is entirely biocompatible, based on the demonstrated biocompatibility of tantalum.

Allowing full mineralization is another preferred property of the present biomaterial. The highly organized process of bone formation is a complex process and is not fully understood. There are, however, certain prerequisites for mineralization such as adequate pore size, presumably larger than 150 microns with interconnect size in the range of 75 microns. A pore diameter of 200 microns corresponds to the average diameter of an osteon in human bone, while a pore diameter of 500 microns corresponds to remodeled cancellous bone. The open cell metal structures of the present invention can be fabricated to virtually any desired porosity and pore size, and can thus be matched perfectly with the surrounding natural bone in order to provide an optimal matrix for ingrowth and mineralization. Such close matching and flexibility are generally not available with other porous implant materials.

One concern with an implant must be the potential for stress shielding. According to Wolff's law, bone grows where it is needed (that is, where there is a stress). Stress on a bone normally stimulates that bone to grow. With an implant, it is primarily the stress/strain field created in the tissue around an implant that controls the interface remodeling. Stress shielding occurs when an overly stiff implant carries stresses that were previously applied to the bone in that area; it can result in inhibition of mineralization and maturation of the ingrowing bone, and/or the resorption of existing natural bone.

An implant, then, must distribute stresses throughout its structure, the ingrowing bone, and the surrounding bone in order to avoid bone resorption and weakening caused by stress shielding. Because metals are stronger than natural bone, this would seem to be a concern with a metallic implant in that the implant would itself focus and bear directly the majority of local loads and stresses that would

ordinarily be placed on the bone, thus depriving both the existing and new bone of those forces which, in effect, help keep it at optimal strength.

The unique structure and properties of the open cell metal structures of the present invention, however, avoid this drawback altogether. The deposited thin films operate as an array within the porous metal body, contributing their exceptional mechanical properties to the structure at large. One result of this effect is that imposed loads are distributed throughout the body. In the case of a open cell metal bone implant, stresses are distributed into both the ingrowing new bone and the surrounding existing bone as well, thereby providing both the old and new bone with the normal, healthy forces they require.

In fact, with the ability to finely tailor the open cell metal structure's properties during the fabrication process, an implant can be designed to distribute stresses in a given direction(s), depending on the needs of the specific application at hand. The bonding of regenerated bone to the implant also helps to transfer stresses directly to the bone in and around the implant; this sharing of biofunction is a consequence of the composite nature of the implant/bone structure. The advantage of these metal structures over other porous implant materials is especially strong in this area. Ceramics lack sufficient mechanical properties to begin with, and no current implant material, either ceramic or metallic, possesses the unique properties of the metal structure as described here.

In the present invention, useful lightweight refractory structures are made by the chemical vapor deposition (CVD) of a small amount of metallic material such as tantalum or niobium (or combination of these materials with other materials to form alloys) into a reticulated (porous) vitreous carbon foam. The density of the resultant body is purposely maintained at substantially below full density, resulting in a structure with extremely favorable properties. The basic approach involves the use of a low-density carbon foam, which is infiltrated with the desired material by CVD to provide uniform thin films on all ligaments. These thin films provide exceptional strength and stiffness to the ligaments, with the expenditure of very little weight. Thin CVD films can provide much higher mechanical properties than can bulk materials. Such quasi-honeycomb materials have remarkably high specific strength and stiffness.

The open cell metal biomaterial structures within a system of the present invention are preferably fabricated using the tantalum metal film and carbon substrate combination, with the film deposited by CVD, to form a structure which mimics bone closely in having open spaces interconnected by ligaments. With the variables available in both the materials and the fabrication process, it is possible to obtain the simultaneous optimization of multiple properties (e.g. strength, stiffness, density, weight) for the given application of substitution for bone.

Another major advantage of the open cell metal structure, when employed in a system of the present invention, is that it is readily shapeable to nearly any configuration, simple or complex, simply by shaping the raw carbon substrate prior to metal infiltration. This facilitates exact contouring of the implant for the specific application and location; precise placement is enhanced and bulk displacement is prevented. Additionally, it appears that any final shaping/trimming needed at surgery can be accomplished on the final device using conventional dental or orthopedic equipment available at the time of surgery.

The optimal conditions for fracture healing and long-term stability can be met if an implant can be designed allowing for motionlessness along all the interfaces necessary for a stable anchorage, thereby excluding (to the greatest extent possible) all outside influences on the remodeling process and allowing the local stress/strain field to control.

Following implantation and initial tissue ingrowth, the metal foam device stays where it is placed without retention aids, and in turn serves to anchor and/or support the cured biopolymer, a reflection of precise contouring and the rapid ingrowth of fibrovascular tissue to prevent dislodgement. The binding between bone and implant, and in turn between implant and biopolymer, stabilizes the implant and prevents loosening. These implants thus will not need to be held in place by other means (e.g. sutures or cement); rather, the growth of a natural bone-to-bone seal is encouraged by the nature of the implant itself. Tissue ingrowth would not be a contributing factor to device retention for a period following implantation, however, until a substantial amount of ingrowth had occurred.

The ability to precisely contour the device, along with its "Velcro-like" surface texture that provides multipoint contact with the surrounding tissue, is of some aid in

retention, although mechanical aids may still be necessary at first. If needed, sutures would seem to lend themselves well to use with the open cell metal structure, while compatibility studies with cement and other bonding aids have been identified as an area of future investigation.

An open cell metal implant, being metallic, will undergo no resorption, and its anticipated complete biocompatibility and osteoconductivity render such concerns moot. Non-resorption is also beneficial in load-carrying applications where complete bone ingrowth cannot be achieved; the continued presence of the tantalum structures, with their superior mechanical properties, is beneficial in such circumstances.

An open cell metal structure for bone implants, for use within a system of this invention, provides an optimal combination of such properties as compatability with the biopolymer, weight, density, strength, biocompatibility, porosity (e.g., high interconnected, uniform, three-dimensional porosity with high void fraction), structure (e.g., similar to natural cancellous bone), osteoconductivity, resorbability, the ability to be fabricated to virtually any desired porosity/pore size, mechanical properties, the ability of imposed loads to be distributed throughout the structure and into both the ingrowing new bone and the surrounding existing bone as well, the ability to avoid stress shielding; and the ability to be shaped to most desired configurations.

Example of Surgical Application

A system of the present invention will be described with reference to a preferred procedure for resurfacing the tibial plateau of the knee, in a manner that provides improved anchoring of the resultant implant by virtue of the use and presence of biomaterial anchor screws as described herein.

With a trocar create two arthroscopic portals antermedial and anterolateral. A third optional portal for irrigation of the joint superpatellar may be created. Inspect all compartments of the knee with the arthroscope. If the knee is tight or the medial joint space is narrow during the scope, an external distractor or fixator may be used (e.g., two AO screws and one connecting rod or a Synthes AO femoral distractor). Place one pin just proximal to the origin area of the medial collateral ligament at distal femur and the other pin the area of the distal insertion site of the ligament (proximal medial tibia). If needed a small outside-in capsulotomy/MCL release may be carried

out through a small stab wound medially. With the scope in the joint, the surgeon should be able to reach all areas of the medial tibial plateau, including the posterior medial meniscus when the external distractor is deployed and the plateau can be placed horizontal to the floor.

The medial tibial plateau is arthroscopically accessed and prepared so as to remove all of the damaged cartilage on the weight-bearing surface of the medial tibial plateau. The anterior edge of the cavity should be located at the level of the initial upslope of the tibial spine, extend mesial to the base of the tibial spine, lateral and posterior to the edge of the tibial plateau. If necessary, the medial meniscus may be debrided back to a stable rim. No lateral meniscal debridement or chondroplasty in the lateral or patellofemoral compartment should be done. Limited synovectomy in the medial compartment should only be done to improve visualization. Remove any fibrillated cartilage and smooth or feather cobblestone and ridged areas on the medial femoral condyle.

Drill at least three (3) anchoring holes to a depth of 5 mm in the subchondral bone. Provide and deliver one or more screws fabricated from a porous material as described above, and secure the screws into the subchrondal bone, e.g., either into previously formed anchor holes, along the surface of the tibial plateau at positions other than the anchor holes, or instead of (and thereby obviating the need for) the anchor holes. The anchor holes can be created in an inverted cone or gourd-shaped geometry to allow for a mechanical lock of the polymer with the subchondral bone once the polymer solidifies. Flex and extend the knee to flush particles from the posterior pouch, superpatellar fossa and posterior fossa. Suction out all areas of the joint with the arthroscope and dry the implant site.

Remove the components of the biopolymer delivery apparatus, including the delivery unit (including the delivery conduit, disc-like mixing path, and shunt tube or reservoir with valve control), body portion, and pre-heated dual barrel biopolymer cartridge from their packaging and place on the sterile field. Optionally, a conventional straight static mixer can be included and used as well, in a preliminary fashion, to facilitate the removal of any air bubbles that may exist in the biopolymer components.

Remove the tip cap from the cartridge and assemble the straight mixer onto the dual barrel cartridge by means of the twist lock. Place the assembly into the administration gun and slowly remove any bubbles by expressing the initial quasi pre-polymer through the straight mixer in a vertical upwards position, expressing 2-3 cc of mixed polymer as waste.

After the bubbles are removed, replace the straight mixer with the disc mixer delivery unit. Ensure that the stainless steel sleeve on the cannula part of the disc mixer is extended to form a straight tip. The stainless steel sleeve is now connected with the advancement mechanism of the administration gun.

Introduce the cannula tip through one portal and retract the stainless steel sleeve. The tip of the cannula is now positioned over the lesion site. Practice reaching all anchor holes with deployed tip to ensure access to all holes. Pay attention to the plane of the tibia in order to allow for the polymer to stay level. With a manual drainage assembly, Set the 3-way valve on the disc mixer such as to discard the mixed polymer through the drainage tubing. Express 3-5 ccs of mixed polymer through drain tubing and stop. Using a plunger-cylinder assembly, a predetermined amount of biopolymer will fill the cylinder, moving the plunger up and opening a direct flow path from the mixing elements to the delivery tip. After manually or automatically shunting biopolymer, begin straight passage of the mixed polymer through the cannula and express the polymer into each of the anchor holes and/or around the secured porous materials, and over the prepared subchondral bone to completely fill the lesion site. While maintaining arthroscopic vision, remove all other instruments from the implant site and allow the material to polymerize to a semi-solid non-tacky state. Withdraw the arthroscope and close the portals (if desired). Keep leg flexed to 90° for 30 minutes post implant (using functional implant and perform a second polymer application. At 30 minutes, extend the leg to zero (0°) degrees in brace. Keep the leg in the extended position for 24 hours.

The patient can be discharged the same day, non weight-bearing locked in extension in brace, and can resume full weight-bearing in 24 hours with brace removed. The patient is recommended to be treated by a physical therapist with range of motion and strengthening exercises for approximately 8 weeks.

The present invention has been described with respect various preferred embodiments, which, together with other conditions and details should not be construed to unduly limit this invention.

CLAIMS

What is claimed is:

1. A surgical system for preparing a composite material *in situ*, the system comprising a flowable, curable biopolymer and a porous, implantable biomaterial adapted to be filled and/or infiltrated by the flowable biopolymer.

2. A system according to claim 1 wherein the biomaterial is provided in the form of an anchor material adapted to be positioned within bone and to permit at least a portion of it to be filled and/or infiltrated with flowable biopolymer in order to provide a mechanical lock between the anchor material and bone.

3. A system according to claim 2 wherein porosity of the biomaterial component is adapted to encourage new bone ingrowth into the composite material over time.

4. A system according to claim 2 wherein the mechanical lock between biopolymer and biomaterial is formed by the infiltration of curing biopolymer into pores of the biomaterial itself and/or by filling the biopolymer into grooves or other structures within the biomaterial.

5. A system according to claim 4 wherein the anchor material mimics the microstructure of natural cancellous bone.

6. A system according to claim 5 wherein the anchor material comprises a reticulated open cell carbon foam infiltrated with tantalum by a process of chemical vapor deposition.

7. A system according to claim 6 wherein the pores of the anchor material are connected to one another to form continuous, uniform channels with no dead ends.

8. A system according to claim 1 wherein the biopolymer comprises a plurality of sterile, flowable parts adapted to be mixed at the time of use in order to provide a flowable composition and to initiate cure.

9. A system according to claim 8 wherein the biopolymer comprises a polyurethane.

10. A system according to claim 9 wherein the polyurethane parts comprise a) a quasi-prepolymer component comprising the reaction product of one or more polyether polyols, one or more isocyanates, and one or more reactive

hydrophobic additives, and b) a curative component comprising one or more polyether polyols, one or more chain extenders, and one or more catalysts.

11. A composite material prepared using a system according to claim 1.

12. A composite material according to claim 11 wherein the biomaterial is provided in the form of an anchor material adapted to be positioned within bone and to permit at least a portion of it to be filled and/or infiltrated with flowable biopolymer in order to provide a mechanical lock between the anchor material and bone.

13. A composite material according to claim 12 wherein porosity of the biomaterial component is adapted to encourage new bone ingrowth into the composite material over time.

14. A composite material according to claim 12 wherein the mechanical lock between biopolymer and biomaterial is formed by the infiltration of curing biopolymer into pores of the biomaterial itself and/or by filling the biopolymer into grooves or other structures within the biomaterial.

15. A composite material according to claim 14 wherein the anchor material mimics the microstructure of natural cancellous bone.

16. A composite material according to claim 15 wherein the anchor material comprises a reticulated open cell carbon foam infiltrated with tantalum by a process of chemical vapor deposition.

17. A composite material according to claim 16 wherein the pores of the anchor material are connected to one another to form continuous, uniform channels with no dead ends.

18. A composite material according to claim 11 wherein the biopolymer comprises a plurality of sterile, flowable parts adapted to be mixed at the time of use in order to provide a flowable composition and to initiate cure.

19. A composite material according to claim 18 wherein the biopolymer comprises a polyurethane.

20. A composite material according to claim 19 wherein the polyurethane parts comprise a) a quasi-prepolymer component comprising the reaction product of one or more polyether polyols, one or more isocyanates, and one or more reactive hydrophobic additives, and b) a curative component comprising one or more polyether polyols, one or more chain extenders, and one or more catalysts.

21. A method of stabilizing an orthopedic implant comprising the steps of providing a system according to claim 1 and employing the system to provide a composite material comprising the anchor material infiltrated and/or filled with cured biomaterial, the composite material being adapted to encourage new bone ingrowth and stabilize the retention of the implant over extended use.

22. A method according to claim 21 wherein the biomaterial is provided in the form of an anchor material adapted to be positioned within bone and to permit at least a portion of it to be filled and/or infiltrated with flowable biopolymer in order to provide a mechanical lock between the anchor material and bone.

23. A method according to claim 22 wherein porosity of the biomaterial component is adapted to encourage new bone ingrowth into the composite material over time.

24. A method according to claim 22 wherein the mechanical lock between biopolymer and biomaterial is formed by the infiltration of curing biopolymer into pores of the biomaterial itself and/or by filling the biopolymer into grooves or other structures within the biomaterial.

25. A method according to claim 24 wherein the anchor material mimics the microstructure of natural cancellous bone.

26. A method according to claim 25 wherein the anchor material comprises a reticulated open cell carbon foam infiltrated with tantalum by a process of chemical vapor deposition.

27. A method according to claim 26 wherein the pores of the anchor material are connected to one another to form continuous, uniform channels with no dead ends.

28. A method material according to claim 21 wherein the biopolymer comprises a plurality of sterile, flowable parts adapted to be mixed at the time of use in order to provide a flowable composition and to initiate cure.

29. A method according to claim 28 wherein the biopolymer comprises a polyurethane.

30. A method according to claim 29 wherein the polyurethane parts comprise a) a quasi-prepolymer component comprising the reaction product of one or more polyether polyols, one or more isocyanates, and one or more reactive

hydrophobic additives, and b) a curative component comprising one or more polyether polyols, one or more chain extenders, and one or more catalysts.

31. A combination comprising a composite according to claim 11 positioned in temporary or permanent touching, or bonded, contact with bone.

32. A combination according to claim 31 wherein the biomaterial is provided in the form of an anchor material adapted to be positioned within bone and to permit at least a portion of it to be filled and/or infiltrated with flowable biopolymer in order to provide a mechanical lock between the anchor material and bone.

33. A combination according to claim 32 wherein porosity of the biomaterial component is adapted to encourage new bone ingrowth into the composite material over time.

34. A combination according to claim 32 wherein the mechanical lock between biopolymer and biomaterial is formed by the infiltration of curing biopolymer into pores of the biomaterial itself and/or by filling the biopolymer into grooves or other structures within the biomaterial.

35. A combination according to claim 34 wherein the anchor material mimics the microstructure of natural cancellous bone.

36. A combination according to claim 35 wherein the anchor material comprises a reticulated open cell carbon foam infiltrated with tantalum by a process of chemical vapor deposition.

37. A combination according to claim 36 wherein the pores of the anchor material are connected to one another to form continuous, uniform channels with no dead ends.

38. A combination according to claim 31 wherein the biopolymer comprises a plurality of sterile, flowable parts adapted to be mixed at the time of use in order to provide a flowable composition and to initiate cure.

39. A combination according to claim 38 wherein the biopolymer comprises a polyurethane.

40. A combination according to claim 39 wherein the polyurethane parts comprise a) a quasi-prepolymer component comprising the reaction product of one or more polyether polyols, one or more isocyanates, and one or more reactive

hydrophobic additives, and b) a curative component comprising one or more polyether polyols, one or more chain extenders, and one or more catalysts.

41. A combination according to claim 31 further comprising natural bone ingrown into at least some of its pores, the composite being positioned within an orthopedic site.

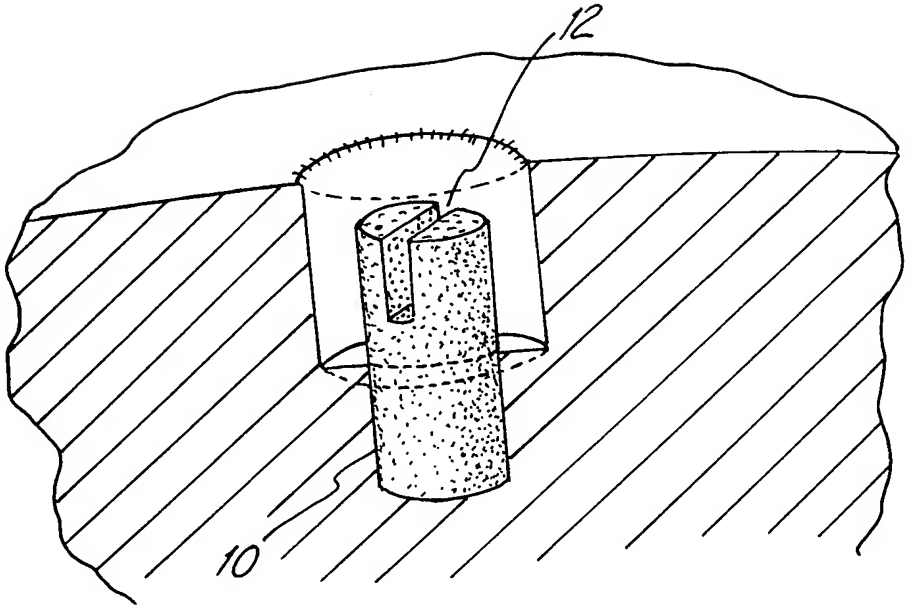

Fig. 1

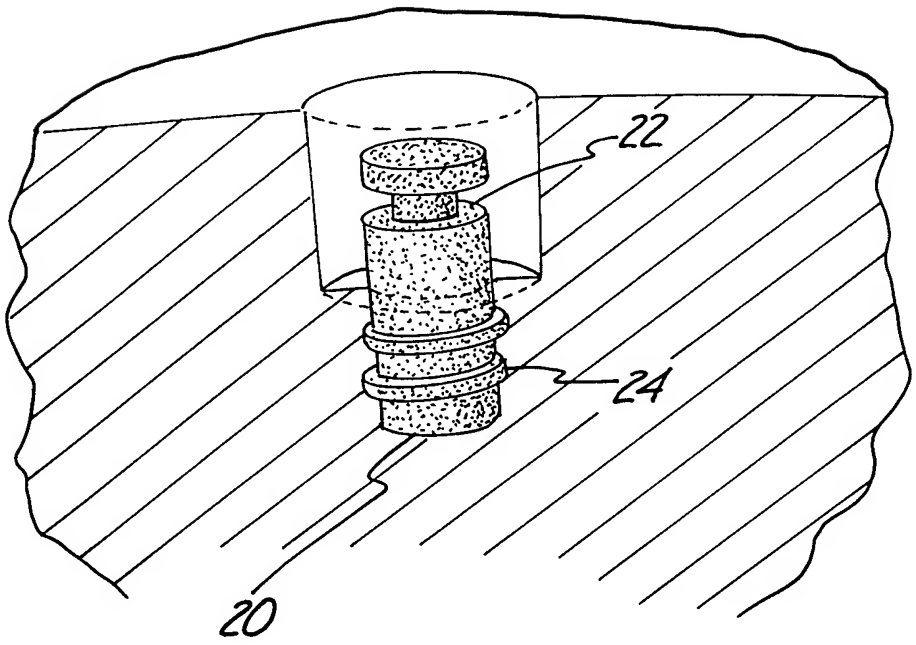

Fig. 2

INTERNATIONAL SEARCH REPORT

International Application No
PC./US 99/10004

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L27/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 282 861 A (KAPLAN RICHARD B) 1 February 1994 (1994-02-01) cited in the application page 3, line 19 - line 42 claims 1,2,4,7,9,10,13,15	1-7, 11-17, 21-26, 31-37,41
A	US 5 556 429 A (FELT JEFFREY C) 17 September 1996 (1996-09-17) cited in the application column 4, line 63 - column 5, line 19 claims 1-14	1,8-11, 18-21, 28-31, 38-41

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 September 1999	15/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Heck, G

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/US 99/ 10004

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 1.1

Although claims 21-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box 1.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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